Research is about answering questions, questions about problems that intrigue you and challenge you, questions that must be capable of being answered. It is therefore all about asking the right questions.

My first research was stimulated by working in a hospital in an industrial town in northern England, where the effects of atmospheric pollution and cigarette smoking combined resulted in large numbers of patients with respiratory failure. I did not at that time know the right questions, but I was helped by Jack Howell, who suggested that I study alveolar CO$_2$ by the rebreathing method. Although there was nothing in it for him, he gave me his time, instruction, and advice freely and started me off on a long and exciting road.

Later, while I was still not sure what I wanted to do, I applied for a job in Birmingham with professor Melville Arnott. I am sure that my brief experience with research into respiratory physiology helped me get that post. The move was entirely unplanned and serendipitous and landed me in a very active department that included Peter Harris. John Butler had recently left, and Donald Heath was in the nearby Department of Pathology. Though a little overawed, I was thrilled at being in such an atmosphere, with constant discussions of ideas, physiological problems, and research techniques. It was a whole new wonderful experience for me. I was given a project—studying the circulatory...
dynamics in chronic bronchitis. Although I didn’t particularly enjoy doing cardiac catheterisations, this was an excellent opportunity to learn about the techniques of gas collection and analysis and the measurement of intravascular pressure and cardiac output. Subsequently I was taught how to do the routine pulmonary function tests for the clinical service and ran this operation for two or three years. In addition I helped run a clinical service and teach medical students.

The point of doing routine clinical and research work is that you gradually learn what the problems really are, and from this base you start to ask the right questions. For clinical research I believe that a basis in routine work is most important in stimulating appropriate questions and in helping place the problems in context.

A little while after I had started in Birmingham someone whom I had not met before turned up at coffee time one morning. He was Gordon Cumming, and he had just returned from working for two years in New York with Gomez. He was talking excitedly about a concept of centrilobular emphysema being a dilatation on the respiratory bronchioles, a critical position for interfering with the movement of gas in and out of the alveoli. He wanted to demonstrate the anatomy of this lesion so that he could study its possible effects but did not know how to do it. I was captivated by his stimulating ideas and intellectual approach and suggested that he make a cast of the airways in emphysema. He replied, “Why don’t you do it?” And so I did. The direction of my future research was sealed at that instant by his best possible of replies.

We made polyester resin casts of the airways in various types of emphysema partly answering the question as to the geometry of the lesions but posing many more questions as to their pathogenesis and physiological effects. It soon became clear that we had no hope of understanding the processes by which gas molecules reach the alveoli in the pathological lung until we understand them in the normal. We decided to switch to studying the normal airways, and I was fortunate to obtain the lungs of a 25-year-old man who had died from nonrespiratory causes. Partly by good fortune and partly by following Tomsett’s advice carefully, we produced a near-perfect cast first time.

Gordon’s continuing advice, discussion, criticism, and refusal to accept the received wisdom as necessarily true saw me through this exciting time and enabled me to develop my own ideas. He was a great facilitator, letting you get on with your own ideas if you had them and stimulating you to think up new ones if you had run out. He always preferred to think about a problem afresh and advised those working with him to read the literature after doing the experiment so as not to be biased by what had been done before.

About this time Gordon bought a copy of a marvelous book, one that was to have a profound effect on my approach to analysing the airway and vascular trees in the lung. The book was Morphometry of the Human Lung, by Ewald Weibel. The demonstration (to me, discovery) that anatomy could be analysed and represented in mathematical terms, by concise formulae and equations, was exciting indeed. I almost devoured the book in my excitement. Like all good intellectual stimuli, it posed exciting questions. What did these mathematical relations mean? How did they come to be there? What other equations were hidden in these structures? I stared at my cast for a long time. There did not seem to be any point in repeating Weibel’s work. Surely these findings must be related to function? While looking at the cast I realised that the size of an airway related in some way to the flow of air it carried.

Generations and Divisions Up

But Weibel’s method of counting generations downward classed together
branches of widely differing diameter and did not seem to relate well to probable function. I hit on the idea of counting upwards instead of downwards, and devised a new (to anatomy) method of classifying the branches (Fig. 1a). Counting starts at the most peripheral branches, which are numbered order 1, and two of these meet to form an order 2 branch. (Originally orders were termed “divisions up”). Two order 2 branches form an order 3 branch, and so on up the tree. When branches of differing orders meet, the order number continues from the higher of the two meeting branches. Thus the longest pathway contains a branch of every order, while the shorter pathways miss some orders.

With great excitement I did a preliminary study of one bronchopulmonary segment, laboriously recording all my data on punch cards. Finally the cards were sorted, the numbers added together, and the plots made. Mean diameter, mean length, and number of branches were all more or less linear on a logarithmic scale against order. This was a new discovery, one that later would prove to be applicable to many different structures.

I continued the work of measuring and counting the airways down to 0.7 mm diameter in all the bronchopulmonary segments and a large sample of peripheral airways from 0.7 mm diameter down to the most distal respiratory bronchioles. This took me 14 months, including many evenings and weekends. It was a labour of love, the prime motivation being that it was to form the basis of my thesis for the M.D. degree (in England this is awarded for research). Without that personal motivation I doubt whether I would have completed the task. The results confirmed the preliminary study, although the plots of log dimension against order were not perfectly linear (Fig. 2). The data could be divided into three zones, within each of which the plots were much more linear.

By counting all of the third generation respiratory bronchioles (RB3) in each sample distal to 0.7 mm diameter branches, an average number of RB3 subtended by branches of 0.4, 0.5, 0.6, and 0.7 mm in diameter was calculated. Having attributed these numbers to each terminal branch on the cast according to size, we could then add the numbers of RB3 all the way up the tree to the trachea. Finally the mean number of RB3 supplied by branches in each order was calculated. This is plotted on a logarithmic scale against order in Figure 3.
and shows a linear relation. Thus the mean number of RB3 increases in constant proportion in successive orders up the tree. If the number of RB3 can be taken as an indication of the quantity of air flowing through a branch, then order is closely related to function.8,9

Pulmonary Artery Cast

Following the success of the bronchial tree analysis, we decided to try to do the same for the pulmonary arterial tree. An Indian research fellow, Siam Singhal, who also wished to work for an M.D. thesis, agreed to try to tackle the job. He was able to produce an arterial cast from a pair of normal human lungs, and this was pruned at 0.8 mm diameter branches, samples of smaller branches down to 0.1 mm diameter being saved for measurement. These samples were photographed, and the measurements were made from the plates by another research fellow, Robert Henderson, from Canada.25

These methods were similar to those used for the airways cast, but this turned out to present serious unforeseen difficulties, throwing doubt on the use of orders in the pulmonary arterial tree. There were two main problems. First, a significant number of arteries branch into three or four daughter branches, and, second, many tiny daughter branches are given off that do not appear to affect the direction or magnitude of the parent branch. If a new order were attributed at each such minor branchings, there would be hundreds of orders in the arterial tree. With some misgivings, I agreed to an arbitrary rule, to ignore branching points where a daughter of less than 0.8 mm diameter was formed. This resulted in loss of information and probably invalidated the ordering.

Denver

At about this stage in the project I left to work in Denver for a year with Professor Giles Filley. Also there were Robert Grover and Wiltz Wagner. Giles gave me a desk to sit at in a room with two American students who were doing research jobs during the summer vacation before going on to study medicine. He provided any facilities I needed but otherwise left me to get on with it. His wisdom and kindness were of great help to me, and my first son was later named for him as a tribute. (We did also like the name!) It was Giles Filley who suggested that “divisions up” should be known as “Horsfield orders.” When our paper was submitted for publication I received some stern criticism from referees for suggesting my own name for this method of ordering. But several other methods of ordering existed, and the eponymous terminology is the simplest way of distinguishing between them.12

I was keen to further the analysis of the airway data that I had brought with me and was able to do this with time to think, free from clinical and teaching interruptions. This was a valuable opportunity that all clinical research workers should try to come by at some stage in their careers.

One of the students with whom I shared the room was Dan Olson, a graduate student in fluid mechanics engineering
and a great enthusiast. We had many discussions relating to British and American society, and Dan subsequently came over to England to do his Ph.D. at Imperial College in London. With him began my education in hydraulics. I was also to reciprocate with medical and physiological knowledge. I believe it to be of the utmost importance that engineers and physicists starting work in physiological research are carefully monitored and tutored to make sure that their work relates to real physiology and not just to a convenient computer model.

In Denver I worked on the problem of how to represent asymmetry in a dichotomously branching tree. The solution, as is so often the case, was simple. After all the branches of a tree have been attributed an order number, the asymmetry at each bifurcation can be quantitatively stated as the difference in order (delta) between the two daughter branches. Where the two orders are the same (delta = 0) the branching is symmetrical with respect to orders (Fig. 4). It is then possible to make a histogram of the distribution of delta for parent branches of each order in the bronchial tree and to find a representative value, which turns out to be 3. A complete model tree (apart from the terminations) can be made using this one value, which gives an average degree of asymmetry, but better models using this principle have different values of delta at different levels in the tree. Various workers have used this method to form asymmetrical bronchial tree models, which have the advantage of being easy to use for calculations because the connectivity is defined.

Much more recently I realised that a tree with a constant value of delta is a fractal, each more peripheral part of the tree being a miniature of the more central branches. Thus the airways do have features suggestive of fractals and can be represented mathematically in this form.

While I was working in Denver, unknown to me an American geographer from Harvard (later Buffalo) had come across our work with the help of Ewald Weibel and arranged a visit to England with Gordon Cumming. A tall, friendly, garrulous, hard-working, enthusiastic man, Mike Waldenberg had been studying the drainage patterns of rivers and had noted the similarities with lung airway and vascular patterns. He suggested using the Strahler method of ordering for pulmonary structures, a method well known in the world of geomorphology (Fig. 1). In this method too the order numbering starts peripherally and carries on up the tree, but order number increases only when two like-numbered branches meet. If two branches of differing order meet, then the next branch up takes the same order as the higher ordered of the two meeting branches (stage 1, Fig. 1b). When all the branches have been thus ordered, contiguous branches of the same order are considered to constitute just one branch (stage 2, Fig. 1c). Thus a branch of a given order may consist of one or of several segments. There are some well marked and important differences between trees ordered by the two methods. A Strahler ordered tree has fewer orders and fewer branches than the same tree when Horsfield ordered, the only exception being a tree with perfectly symmetrical branching (i.e., when delta = 0 throughout) when both methods give the same result.

The great advantage of Strahler’s
method is that the minor branches of the pulmonary vessels, just like the minor streams that join rivers, do not affect the order number of their parent branch. Thus, at a stroke, the main worry that I had had about ordering our pulmonary artery data was removed—in my absence and without my knowledge! Mike and another fellow at Birmingham, Keith Harding, relabeled and reanalyzed all the data in terms of Strahler orders. The results were plotted using a logarithmic scale for mean diameter, mean length, and number of branches in each order against order number (Figs. 5 and 6).

Because the plots for diameter and length are much more linear with Strahler orders than with Horsfield orders, a slope to the line can be more confidently attributed. These slopes, expressed as positive numbers, are known as the diameter ratio, the length ratio, and the branching ratio, respectively, for the diameter, length, and number plots. These ratios are the factors by which mean diameter, mean length, and number of branches increase in successive orders in the tree.\textsuperscript{10}

Strahler ordered trees of many kinds, such as rivers, glaciers, bile ducts, arteries, veins, Purkinje cells, and botanical trees\textsuperscript{1,32} show similar features when plotted in this way. Because of this, Strahler orders have been used to compare trees between species\textsuperscript{15,16} and within species\textsuperscript{10} and to study growth.\textsuperscript{5,14} However, much information is lost in the simplification involved in Strahler ordering, especially the connectivity, that is, the way in which the various branches join together. Because of this, Strahler ordered trees are not good for making physiological calculations.

This is an appropriate point to consider where generations, as used by Ewald Weibel, fit into this scheme. The counting of generations starts at the main stem, trachea, or pulmonary artery and contin-
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ues outward. The generation number is thus a statement of the position of a branch within the tree with respect to the stem. Applied to pathways, it is a measure of their lengths, and a plot of the distribution of generations to terminal branches is an expression of the asymmetry of the system. This approach looks at the tree as a divergent system and is particularly helpful in describing its structure. In contrast, the methods of ordering look at trees as convergent structures, most obviously thought of in these terms are rivers and venous trees in which flow is toward the main stem. The order number is not a statement of position in the tree, for branches of a given order can be found at various distances from the stem. The number is, however, much more closely related to function, as branches of a given order supply similar subtrees and have smaller ranges of diameters than do branches within a generation. Thus the two methods are simply looking at different aspects of the same thing and are not in conflict with each other.

Return to Birmingham

By the time I had returned to Birmingham from Denver, Mike Waldenberg had left, and I had to await his next visit before meeting him. He returned most years after that, sometimes twice a year, during the university vacations to work with us on the properties of branching trees and the flow fluid in them. I am not aware of any other instance of a geographer and a physician cooperating on basic research in the lung. Our association has lasted 21 years, has been full of interest, and has resulted in a number of published papers. However, a proportion of my published work has been based on, or has incorporated, ideas originating from Mike without his name being included among the authors. This has been an unintentional injustice, and I would like to take this opportunity to acknowledge his great contribution to my research efforts and to state that it would have been proper for his name to have appeared on several papers I wrote without him.

This brings to mind a point on authorship of papers. I have never found it disadvantageous to include someone’s name on a paper when that person has made any contribution toward it. Several times I have asked someone to be a coauthor who has declined; this is fine and no one is offended. But if you leave off the name of someone when that person thinks that they should be included, then unnecessary resentment and bitterness may ensue.

The Midhurst Medical Research Institute

A little while after my return from the United States we heard that an anonymous donor had given the sum of 5 million pounds to set up a new research institute at the King Edward VII Hospital at Midhurst in Sussex. Subsequently, Gordon Cumming was appointed medical director, and he asked me to be deputy medical director. Many members of the medical establishment were strongly opposed to siting a major institute outside of London in the beautiful countryside of Sussex. But the donor insisted that his institute should go there or nowhere. At the time he was a patient of the hospital, and I believe he hoped that putting a research institute there would improve the hospital’s standing and help put it in the front line of British hospitals. We had the wonderful experience of helping design, seeing built, and equipping the Midhurst Medical Research Institute to our own specifications. Her Majesty the Queen officially opened the building on November 2, 1973.

However, there were many difficulties. One was trying to meld the staff member of the hospital, who had no experience of the
academic world and were therefore highly suspicious of it, with the academic staff of the institute. In my view, this was never achieved. Another problem was the geography. King Edward VII Hospital had been founded as a tuberculosis sanatorium, a function it performed with worldwide distinction. But it was isolated, well away from all teaching hospitals, and difficult for patients to get to. The donor died, and the chairman of the Board of Governors negotiated our takeover by the Cardiothoracic Institute in London. Three years later the Midhurst Medical Research Institute closed, 14 years after it had opened, and our foundation passed to the Cardiothoracic Institute, now the National Heart and Lung Institute. In retrospect, I believe we were doomed from the start. The donor had, with the very best of motives, ignored the advice of the medical profession regarding the siting of the institute. Once he had died, only those who worked there thought that it should continue at Midhurst. Gordon Cumming, who had wanted to leave a viable institute behind when he retired, had to witness its closing as he left. It was an unhappy end to his career and to what had been a promising new project.

At Midhurst we produced a steady flow of papers, predominantly in the cardiac and respiratory fields. Only a few of them were clinically oriented. I finished the work I started in Birmingham of measuring branches of the pulmonary artery from 100 µm down to 13 µm diameter, thereby completing a sample of Strahler ordered data for the full range of diameters. From these data a complete Strahler ordered model of the pulmonary arterial tree was developed, shown in Figure 6.6

I was lucky in that I had made an almost complete cast of the tree, using the “anatomical resin” described by Tompsett.26 Following a political disruption of our oil supplies (oil being used in the manufacture of polyester resins), the manufacturers ceased making this resin. No other has proved to be as satisfactory for making anatomical casts, and I am certain that I would not have had as good a cast to study had I not made it when I did.

### Venous Cast

At a later date it was decided to make a study of the human pulmonary venous tree. This turned out to be a much more complicated business. For the cast to remain in one piece, it must include the left atrium, which can be cannulated via the left ventricle. Our anatomical resin had run out, and the substitute was decidedly inferior. The quality of the venous casts in no way approached that of our arterial cast but was just sufficient to make measurements down to 0.2 mm diameter. From these data we constructed a dimensional model of the venous tree, shown in Figure 7.13

![Figure 7. Strahler ordered data for a cast of the human pulmonary venous tree, represented in the same way as in Figure 6. Note that there are two fewer orders than in the arterial tree, as four pulmonary veins join the left atrium, which thus represents two orders. From branches of 0.2 mm downward, the points were obtained by both extrapolation and interpolation.](image)
Murray and Optimization

It was Mike Waldenberg who introduced me to the work of Murray, published in 1926. Murray had looked at optimization of arterial diameters to minimize power (work per unit time) using the following approach. To minimize the resistance to flow, the arterial diameters should be maximized. But to minimize the metabolic work of maintaining the tissues of the arterial wall and the blood within them, the diameters should be also be minimized. To minimize total power output, the diameter should have some optimal value, probably related to the flow it has to carry, as vessels carrying larger flows are likely to have greater diameters. Murray showed that in an ideal situation, where perfect laminar flow occurs and Poiseuille's equation holds, flow is proportional to diameter cubed when the total power output is minimum. This idea was taken further by Uylings, who showed that if turbulent flow were fully developed, for power to be minimum, flow would have to be proportional to diameter to the power of 2.3. The exponent, that is, the value 3.0 in the first case and 2.3 in the second, we called $z$.

What value of $z$ is found in the arterial trees in the body? Mayrovitz and Roy measured flow and diameter in directly observed peripheral systemic arteries and found that $z = 3.01$, a remarkable confirmation of the efficient “design” of the arteries predicted 57 years earlier. Mike and I decided that it would be fascinating to find the value of $z$ in the pulmonary arterial tree. We could not have flow measurements in individual arteries, but, fortunately, if the diameters of the three vessels meeting at a bifurcation are known, than $z$ can be calculated for that junction. We measured the diameters at 1,937 bifurcations on the two casts we had previously used for arterial studies and found that $z = 2.3 \pm 0.1$. The immediate implication seemed to be that pulmonary arterial diameters are optimized for fully developed turbulent flow. But further study of the subject denied this. Although the main pulmonary artery has a Reynolds number (which gives information as to the type of flow) of over 2,000, this rapidly diminishes in the smaller vessels, and turbulent flow, even in the main arterial trunk is unlikely.

This value of $z$, which we had found in a previous smaller study, is intriguing and tells us that the pulmonary arterial tree is optimized for other factors in addition to straightforward minimum power. If the diameters of the higher ordered branches are increased, the calculated value of $z$ falls. Larger diameters in the higher orders could be advantageous in reducing acceleration of the blood during systole, reducing turbulent flow, and giving a reservoir function to the vessels. The latter allows much of the blood expelled from the right ventricle during systole to be accommodated in the larger elastic vessels and to be expelled gradually during the remainder of the cardiac cycle, maintaining a fairly steady flow. These functions are not required in the small systemic arteries in which $z$ was found to be close to 3.0.

Using the same data, we plotted the summed cross sectional area of the two daughter branches at each bifurcation against the cross sectional area of the parent branch on logarithmic scales (Fig. 8). The linear relation, parallel to and slightly above the line of identity, indicates that the cross sectional area of the arterial tree increases by an average value of 1.0879 at each bifurcation and that this value is independent of the position of the bifurcation in the tree.

How is the diameter of a branch adjusted to meet these requirements? First, a genetic factor must control diameters to be somewhere near the ideal. But just as muscle and bone can respond to applied stress by growth, so can the branches of the arterial tree adjust their diameters in re-
Optimality and Branching Angles

Mike and I also looked at optimality in relation to angles of branching. Consider a triangle ABC (Fig. 9). If a branch originates at A and bifurcates at D so that the two daughter branches go to B and C respectively, then the minimum sum of length of the three branches occurs when the branching angle is 120° between each pair of branches. This is true whatever the shape of the triangle. In our analysis a “cost” is attributed to each branch, and this cost has to be minimized. In the above example the cost is the length of the line. More realistically, suppose the cost is volume that has to be minimized and that the branches each have different diameters. Then at the minimum the larger of the two daughter branches will deviate from the line of the parent with the smaller angle and from the smaller branch with the larger angle (Fig. 10). This pattern of branching is observed in the majority of bifurcations in the bronchial, venous, and arterial trees and confirms that optimization of angles of branching of some kind is operating.

Other cost principles have been studied, including surface area, drag, and power dissipation. The latter two are not
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0

Figure 10. General form of a typical bifurcation. Parent branch 0 gives rise to the two daughter branches 1 and 2. $D_0 > D_1 > D_2$ and $\theta_2 > \theta_1$, where $D =$ diameter and $\theta =$ branching angle.

only a function of diameter but also of the value of $z$. Knowing the diameters of the three branches at a bifurcation from which $z$ can be calculated, one can calculate an ideal branching angle for each cost function and compare it with that observed. These techniques were developed to provide a methodology for studying optimality in branching angles; they have not yet yielded any clear answers.

These studies of optimality of diameters and branching angles and their relation to flow may seem esoteric and theoretical. But they give great insight into the “design” of the airways and blood vessels and the relation between structure and function in these trees. They also provide a basis for future haemodynamic studies. The word “design” is in quotes. Given that the lung evolved, each evolutionary change in structure that gave a biological advantage to its owner was more likely to survive. Thus, over many years the lung became a more efficient organ for gas exchange. But this does not mean that the most efficient possible design has evolved, only that of those tried so far, the most efficient are probably those that have survived.

Conclusion

A glance at a cast of the airways or blood vessels of the lung shows that these structures are well adapted for distributing and bringing together air and blood in the capillary network so that gas exchange may occur. The way in which these structures are adapted to their task has proved to be a fascination for me for nearly 30 years, and studying them has been a great pleasure. The people with whom I have worked have both allowed and helped me get on with the research that I wanted to do. In this I recognise that I have been extremely lucky, and to those who have facilitated my path I am most grateful.

References

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